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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/666,430 | 09/21/2000 | Delphine Gabrielle Josette Rea | 4205.1US | 6289 |

7590 12/27/2004

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| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | |

DATE MAILED: 12/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/666,430 | REA ET AL. | |
| | Examiner | Art Unit | |
| | G. R. Ewoldt, Ph.D. | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11/21/03, 5/18/04, 10/04/04*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 40-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1 and 40-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 11/21/03
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

**DETAILED ACTION**

1. Applicant's amendment, responses, and 1.132 declaration of Inventor Offringa, filed, 11/21/03, 5/18/04, and 10/04/04 are acknowledged.

2. In view of Applicant's response the restriction requirement has been withdrawn.

Claims 1 and 40-68 are being acted upon.

3. Applicant is advised that the substitute specification filed 3/18/03 has not been entered because no marked-up copy of the specification has been submitted.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1 and newly added Claims 40-68 stand/are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for,

the *in vitro* induction of non-responsiveness of MHC-matched clonal T cells to a defined antigen when dexamethasone-treated dendritic cells have been loaded with the same defined antigen,

does not reasonably provide enablement for,

*in vivo* or *in vitro* induction of non-responsiveness of polyclonal T cells to any undefined antigen or the *in vivo* induction of non-responsiveness when an "unwanted T-cell response" is ongoing, for the reasons of record as set forth in papers mailed 6/29/01, 9/19/02, and 5/21/03.

Applicant's arguments, filed 11/21/03, have been fully considered but they are not persuasive. Applicant argues, "The applicants respectfully submit that the Office Action appears to indirectly put forward the position that the *in vitro* data of the specification does not support claims to *in vivo* uses."

The Examiner's position is simply that the data disclosed in the instant specification (and newly provided 1.132 declaration) provides insufficient support for the method of the instant

claims. *In vivo* data is not required, however, an enabling specification is required.

Applicant argues "The examples provided in the declaration demonstrate unequivocally the use of the alternatively stimulated dendritic cells as a pharmaceutical composition *in vivo* (page 3 of Paper 15). The alternatively activated dendritic cells are capable of inducing a prolonged skin graft survival when administered as a pharmaceutical composition *in vivo* to mice having undergone a skin graft with an incompatible donor-recipient combination." In Applicant's remarks it is asserted that the DCs in the example present the same antigens as the skin graft cells; Hancock et al. 1996 is cited in support.

Neither the single relevant example of the specification (Example 4), nor the newly provided data of the Inventor's 1.132 declaration, actually address the invention of the instant claims. Example 4 merely discloses that a T cell response to a known antigen can be reduced employing a known immonosuppressive drug (Dex). The Inventor's declaration provides little additional enablement for the claimed method. Example 1 teaches that an *in vitro* alloimmune T cell response (MLR) can be suppressed employing Dex-treated DC. Example 2 teaches that a long term cultured Dex-treated DC (not a cell that could be employed for *in vivo* treatment) could reduce an allo-response.

The examples fail to demonstrate how the antigens associated with the unknown T cell responses are established and employed to reduce an unwanted T cell response. Note that the example of the specification discloses only a known antigen that is not associated with any known unwanted T cell response, and the examples of the declaration are not antigen specific - alloimmune responses are not considered to be antigen-specific responses. Regarding the assertion that the DCs in the example present the same antigens as the skin graft cells, Applicant provides no evidence of this and no evidence that an antigen-specific unwanted T cell response is reduced. Regarding Hancock et al. 1996, the reference teaches the importance of CD40-CD40L interactions in allograft rejection. Applicant's assertions as to the "presumptions" of the authors (regarding alloantigens) comprises nothing more than an attorney's assertion which is not found to be convincing. Accordingly, the submissions of record comprise insufficient support for a method comprising the reduction of an unwanted antigen-specific T cell response.

Applicant argues "An advantage of the invention is that the exact identity of all possible antigens is not required.

Therefore, the invention is not limited to the use of any specific antigen. A person of ordinary skill in the art would recognize that professional antigen presenting cells (APCs), such as dendritic cells, can be loaded with any antigen for which tolerization is desired... Thus, loading of an antigen may be accomplished by bringing dendritic cells into contact with any antigen source for which tolerization is desired".

Applicant's argument is a bit confusing; it is unclear how dendritic cells can be loaded with any antigen for which tolerization is desired if the identity of said antigens has not been established.

Applicant argues, "Furthermore, antigens for specific diseases are known in the art. For examples multiple sclerosis is a demyelinization disease, associated with an autoimmune response to the myelin basic protein." Nicholson et al., Greten et al., and Stemme et al. are cited in support.

Applicant's assertion that, "antigens for specific diseases are known in the art" comprises a severe oversimplification of a complex line of investigation. Greten et al. merely speculates that HTLV-1 Tax 11-19 CD8+ T cells "play a pivotal role" in the neurological pathogenesis sometimes seen with HTLV-1 infection., and Stemme et al. merely states that "oxLDL is potentially significant" in atherosclerosis. Nicholson et al. speculates that heteroclitic APLs "may have a role in the initiation of autoimmunity". None of these references provide any definitive statements regarding T cells specific for the described antigens being absolutely known to be pathogenic in the described diseases.

Probably the most well-studied of the presumed pathogenic autoantigens is MBP. MBP-reactive T cells from MS patients have been isolated, and methods for both inducing T cell tolerance to MBP and reducing the number of said cells have been tried. Neither method provided an effective treatment for the disease (see *Marketletter*, 1999 and Zhang et al. 2002). Note that in Zhang et al. it is established that the number of MBP-reactive T cells has been reduced (Figure 1), but even the authors' tortured evaluation of data leaves them with the finding that while depletion of said cells might initially "coincide" with "slow progression", disease progression "seemed to accelerate" after 12 months.

Thus, it remains the Examiner's position that the specification fails to adequately describe how to make and use

the method for producing antigen-specific tolerized T cells for the reduction of unwanted T cell responses as set forth in the instant claims.

6. Claims 1 and newly added claims 40-68 stand/are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

As set forth previously, there is insufficient written description to show that Applicant was in possession of "means for reducing IL-12p40 production by said dendritic cell" or "means for causing said dendritic cell to secrete IL-10 in vitro", other than dexamethasone. As said "means" comprise an unknown genus of indeterminant size, one of skill in the art must conclude that the specification fails to disclose an adequate written description or a representative number of species to describe the claimed genus. Likewise, the specification discloses *no* specific "antigen[s] against which said T-cell response is to be reduced". Again, given the indeterminant size of the claimed "antigen" genus, and in this instance *no* species of the genus are disclosed, one of skill in the art must conclude that the specification fails to disclose an adequate written description or a representative number of species to describe the claimed genus.

Applicant's arguments, filed 11/21/03, have been fully considered but they are not persuasive. Applicant argues that, "the specification provides a written description for a means of reducing IL-12p40 production and a means of causing dendritic cells to secrete IL-10 *in vitro*". Applicant cites 35 U.S.C. 112, paragraph six.

Applicant is advised that no rejection under 35 U.S.C. 112, paragraph six has been made. It remains the Examiner's position that the single "means for reducing IL-12p40 production and a means of causing dendritic cells to secrete IL-10 *in vitro*" disclosed in the specification, i.e., culturing DC in Dex, comprises an insufficient description of the broadly claimed invention.

Applicant argues, "The rejection appears to the applicants to require a written description of every, or at least

a large number of representative examples of member [sic] of the phrases at issue. The applicants respectfully submit that an adequate written description imposes no such requirement".

Applicant is advised that a representative number of examples is required. Said representative number can only be established in relation to the genus in question. It remains the Examiner's position that a single example is not a representative number of examples of the genus in this instance.

Applicant argues that the new claims reciting "a substance capable of activating a glucocorticoid receptor" are adequately described. Applicant further argues that Dex is representative of a substance capable of activating a glucocorticoid receptor.

Applicant is advised that the single substance capable of activating a glucocorticoid receptor disclosed in the specification, i.e., Dex, is not considered to be a representative number of examples of the claimed genus of *all* substances capable of activating a glucocorticoid receptor. Applicant is reminded, as set forth previously, that the term must be given its broadest reasonable interpretation, such as set forth in *Stedman's Medical Dictionary* (2002) wherein glucocorticoid is defined as "any steroid-like compound capable of significantly influencing intermediary metabolism." And further wherein, "intermediary metabolism" is defined as "the sum of all metabolic reactions between uptake of foodstuffs and formation of excretory products."

Applicant argues that, regarding the term "antigen", "The invention may be used in combination with any antigen which causes an unwanted immune response that the subject needs to be tolerized for".

It remains the Examiner's position that the specification fails to adequately describe a representative number of said antigens. Applicant is advised that this is not a rejection for lack of enablement, in this instance it is not *how* the antigens are used but *which* antigens are to be employed.

7. The following are new grounds for rejection necessitated by Applicant's amendment.

8. Claims 40-68 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the

inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) A substance capable of activating a glucocorticoid receptor (Claims 40 and 51-55)

B) A method for preparing an isolated dendritic cell, said method comprising:
isolating peripheral blood monocytes from a subject;
culturing the peripheral blood monocytes to differentiate into dendritic cells;
activating the dendritic cells with a glucocorticoid;
loading the dendritic cells with an antigen; and
isolating said loaded, activated dendritic cells (Claim 56).

C) The method according to claim 56, wherein the antigen comprises an allogeneic antigen (Claim 59).

D) A method for obtaining a dendritic cell capable of tolerizing a T-cell or tolerizing a T-cell in a graft or transplant recipient (Claims 64 and 65).

Regarding A) the specification supports binding but not activating.

Regarding B) the specification does not disclose this generic method for preparing any type of isolated DC.

Regarding C) the specification does not disclose the generically-claimed method employing a generic allogeneic antigen.

Regarding D) the specification discloses only tolerizing T cells to an antigen and not tolerizing a generic T-cell or tolerizing a T-cell in a graft or transplant recipient.

9. No claim is allowed.

10. The references on the IDS submitted 11/21/03 have been numbered 1-12. References 1-5 and 12 have been lined through and have not been considered because they have been improperly or incompletely cited. See MPEP 609.

11. Applicant's amendment or action necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of

the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805. The examiner can normally be reached Monday through Thursday from 7:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Technology Center 1600 at 703-872-9306 (before final) and 703-872-9307 (after final).

12/22/04

G.R. EWOLDT, PH.D.
PRIMARY EXAMINER

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May 20, 2003